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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,531	07/11/2003	Philip A. Furman	04674.105074 (TRI 1016)	6903

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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1619	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,531	FURMAN, PHILIP A.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8 have been examined on the merits.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 7, 2010 has been entered.

Claims 1-8 are pending in this application.

Claim Rejections - 35 USC § 103

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schinazi et al. U.S. Patent No. 5,703,058 A and Thyagarajan U.S. Patent No. 6,589,570 B1 and in further view of Delaney et al. (Antiviral Chemistry & Chemotherapy, 2001) (U)

The claims are drawn to a method for treatment or prophylaxis of a human infected with Hepatitis B virus comprising administering an effective amount of β-L-FTC, L-FMAU and interferon.

Schinazi et al. teach **FTC** exhibits activity against Hepatitis B virus (HBV) (column 2, lines 40-41) and genetically engineered vaccine, **alpha interferon** effective for HBV (column 2, lines 46-55). Schinazi et al. further disclose that **L(-)FMAU** is an example of an antiviral agent that can be used in combination with the (-) enantiomer of FTC (column 6, lines 21-27) for the treatment of HBV infections in humans (column 3, lines 5-6).

It does not specifically teach all three agents to be combined into one combination treatment to be administered, however Schinazi teach that the agents recited in claim 1 of the patent are to be administered in combination or in alternation with a second compound.

Schinazi teaches that FTC exhibits activity against **HBV** and alpha interferon is effective for **HBV** and that L(-)FMAU is an example of an antiviral agent that can be used in combination with the (-) enantiomer of FTC (column 6, lines 21-27) for the treatment of **HBV** infections in humans (column 3, lines 5-6).

Delaney et al. teach L-FMAU and FTC are new nucleoside analogues (page 3, column 2) and teach that the preexistence of variants (viral mutations) with the potential to resist two drugs is assured, preexistence of resistance to three or more drugs is unlikely. This implies that the in vivo antiviral effect of drug combinations that contain two drugs will be dramatically increased by the addition of an third. This phenomenon has been described as the "Combinatorial ledge" and provides the theoretical basis for the use of at least three antiviral drugs in current "highly active antiretroviral therapy" (HAART) regimes which are used against HIV. Furthermore, there is a sound

theoretical basis for combining two or more nucleoside analogues with immune modulators and/or inhibitors of de novo nucleotide biosynthesis (page 27, column 1). Delaney et al. concludes that combination chemotherapy using nucleoside and or nucleotide analogues with different resistance profiles provides a conceptually promising approach for the long-term control of drug resistance (page 28, column 1). Delaney et al. does not specifically teach the combination of L-FMAU and FTC with interferon. However Schinazi teaches that L(-)FMAU is an example of an antiviral agent that can be used in combination with FTC as stated supra and further teach the activity of alpha interferon against HBV. One having ordinary skill in the art would have been motivated to combine L(-)FMAU, FTC and interferon motivated by the teaching of Schinazi that that L(-)FMAU is an example of an antiviral agent that can be used in combination with the (-) enantiomer of FTC (column 6, lines 21-27) for the treatment of **HBV** infections in humans (column 3, lines 5-6) and would be further motivated to add another effective agent, such as interferon motivated by the teaching of Delaney et al. who teach , there is a sound theoretical basis for combining two or more nucleoside analogues with immune modulators and/or inhibitors of de novo nucleotide biosynthesis and that combination chemotherapy using nucleoside and or nucleotide analogues with different resistance profiles provides a conceptually promising approach for the long-term control of drug resistance.

One of ordinary skill in the art could have combined the elements as claimed by known methods and that in combination, each element merely would have performed the same function as it did separately, to treat or prophylax against HBV.

One of ordinary skill in the art would have recognized that the results of the combination were predictable.

The convenience of putting the β-L-FTC, L-FMAU and interferon together in one composition for the method of treating/prophylaxing against HBV, though perhaps a matter of great convenience, did not produce a new or different function and to those skilled in the art, the use of the old elements in combination would have been obvious. The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945).

Schinazi et al. does not teach the β-L-FTC is substantially pure and it does not teach the many variations of interferon.

In general, stereoisomers/optical isomers are obvious from racemic mixtures. As legal authority the examiner cites *In re Adamson and Duffin,* 125 U.S.P.Q. 233. The case sets forth the requirements of patentability with regard to stereoisomers as follows:

1) The existence of a racemate is, in and of itself, sufficient to render obvious any individual stereoisomers contained within; no express suggestion of isomer separation is needed. See the first paragraph on page 235.

2) One skilled in the art expects that individual stereoisomers will differ significantly in physiological/pharmacological activity and toxicity, because living systems are chiral and thus preferentially process stereochemical configurations over others.

See page 234, the third full paragraph and page 235, the fifth full paragraph on the page.

L-FTC is known from the recitation of its use for treatment of HBV in Schinazi et al. Consonant with the reasoning of *Adamson*, the existence of that racemate renders obvious any individual stereoisomers contained within, i.e. the R and S enantiomers recited instantly. Regarding the substantially pure form of β-L-FTC, Schinazi et al. teach that the β-L forms are specifically contemplated (column 7, line 64 to column 8, line 3). Schinazi teach that enantiomerically pure forms are used herein and the term enantiomerically enriched refers to a nucleoside composition that includes at least 95% to 98% of a single enantiomer of that nucleoside (column 6, lines 45-49). One skilled in the art would have been motivated to prepare additional useful compositions of the ranges taught by the prior art. While the reference is silent regarding the 90% by weight ratios, the difference in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. When the general conditions are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 45, 105 USPQ 233, 235 (CCPA 1955). In the absence of any criticality and/or unexpected results of the additional ranges claimed, the instant invention is considered obvious.

Regarding the method of use of alpha, beta and gamma interferon for the method of treating hepatitis B, Thyagarajan (quoting Lau et al., Gut. Suppl. 1991;547-562) recites in Table 1 (column 2), agents that have been studied and are successful in

the treatment of HBV infection are *inter alia* interferons such as Alpha interferon, Beta interferon and Gamma interferon.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ the combination of β-L-FTC and L-FMAU and interferon for the treatment or prophylaxis of a human infected with hepatitis B virus motivated by the teaching of Schinazi et al. who recites that L(-)FMAU is an example of an antiviral agent that can be used in combination with the (-) enantiomer of FTC (column 6, lines 21-27) for the treatment of HBV infections in humans (column 3, lines 5-6) along with alpha interferon (column 2, lines 46-55) and the teaching of Thyagarajan who recites that interferons such as Alpha interferon, Beta interferon and Gamma interferon are successful treatments for HBV.

Response to Arguments

Applicant's arguments with respect to claims 1-8 have been considered but are moot in view of the new ground(s) of rejection.

Applicant disagrees with the rejection because the pending claims recite a method for the treatment or prophylaxis of a human infected with HBV comprising administration of β-L-FTC and L-FMAU and interferon or pharmaceutically acceptable salts of any of the above and states that the claimed method provides several unforeseen advantages for the treatment of hosts infected with HBV. Applicant states that the results from the *in vivo* experiments using the woodchuck model of HBV infection induced remarkably rapid reduction of the viral load which is significant

compared to results obtained with β-L-FTC or L-FMAU. Applicant states that Schinazi describes sixteen genuses of compounds for use in treating HIV and HBV infections and these compounds may be used in combination with a second antiviral agent and states that Schinazi does not provide data on any combination therapy. In response, Schinazi et al. specifically teach that **FTC** exhibits activity against Hepatitis B virus (HBV) (column 2, lines 40-41) and genetically engineered vaccine, **alpha interferon** effective for HBV (column 2, lines 46-55). Schinazi et al. further disclose that **L(-)FMAU** is an example of an antiviral agent that can be used in combination with the **(-) enantiomer of FTC** (column 6, lines 21-27) for the treatment of HBV infections in humans (column 3, lines 5-6). Schinazi et al. does not specifically teach all three agents to be combined into one agent to be administered, however, as stated supra, Delaney et al. teach L-FMAU and FTC are new nucleoside analogues (page 3, column 2) and teach that the preexistence of variants (viral mutations) with the potential to resist two drugs is assured, preexistence of resistance to three or more drugs is unlikely. This implies that the *in vivo* antiviral effect of drug combinations that contain two drugs will be dramatically increased by the addition of an third.

Schinazi teach that the agents recited in claim 1 of the patent are to be administered in combination or in alternation with a second compound. As stated in In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980):

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); In re Crockett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in

Crockett, the idea of combining them flows logically from their having been individually taught in the prior art.

In this case, each of the agents are individually disclosed to be used in combination for the treatment of hepatitis. It would have been obvious for one having ordinary skill in the art at the time the invention was made to employ interferon, L(-)FMAU and L-FTC in combination to treat the same disorder. In keeping with the flexible nature of the obviousness inquiry, *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 [82 USPQ2d 1385] (2007), ***the requisite motivation can come from any number of sources and need not necessarily be explicit in the art***. See *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 [84 USPQ2d 1198] (Fed. Cir. 2007). Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship … to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Id*. (quoting *Dillon*, 919 F.2d at 692). In this case, all of the agents are known individually to treat hepatitis B virus and the idea of combining them flows logically from their having been individually taught in the prior art.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thyagarajan is cited for teaching agents that have been studied and are

successful in the treatment of HBV infection are *inter alia* Interferons such as Alpha interferon, Beta interferon and Gamma interferon (Table 1, column 2). Applicant states that the Examiner ignores the fact that the drugs may be inactive, antagonistic or cause new side effects if combined. In response, as stated supra, Delaney et al. provides evidence that three or more agents provide an advantage in treatment of hepatitis B teaching that a "Combinatorial ledge" provides the theoretical basis for the use of at least three antiviral drugs in current "highly active antiretroviral therapy" (HAART) regimes which are used against HIV. Furthermore, there is a sound theoretical basis for combining two or more nucleoside analogues with immune modulators and/or inhibitors of de novo nucleotide biosynthesis (page 27, column 1). Delaney et al. concludes that combination chemotherapy using nucleoside and or nucleotide analogues with different resistance profiles provides a conceptually promising approach for the long-term control of drug resistance (page 28, column 1).

Applicant cites post filing date, Osborn as evidence of antagonism occurring with combination therapy of two nucleoside compounds, telbivudine and lamivudine. In response to applicant's argument it is noted that the agents that applicant argues (i.e., the combination of telbivudine and lamivudine) are not recited in the rejected claim(s). Further, as stated supra, Schinazi et al. teach **FTC** exhibits activity against Hepatitis B virus (HBV) (column 2, lines 40-41) and genetically engineered vaccine, **alpha interferon** effective for HBV (column 2, lines 46-55). Schinazi et al. further disclose that **L(-)FMAU** is an example of an antiviral agent that can be used in combination with the (-) enantiomer of FTC (column 6, lines 21-27) for the treatment of HBV infections in

humans (column 3, lines 5-6). Schinazi et al. does not state that these agents are antagonistic as Applicant implies. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./
Examiner
Art Unit 1619

September 28, 2010
/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619